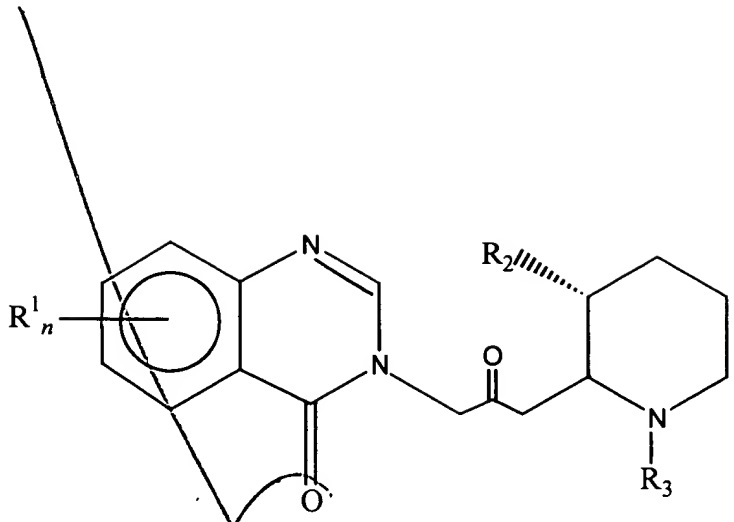

A2 cont.

wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

REMARKS

Applicant submits herewith as Exhibit A, a complete set of claims marked to show all amendments and as Exhibit B, a complete set of amended claims in clean form containing all the amendments. No new matter has been added by the amendments.

RESPONSE TO THE RESTRICTION REQUIREMENT

In the Office Action of December 13, 2001, at page 2, the Examiner has presented a three-way restriction of Applicants' invention, as between:

I. Claims 1-28, drawn to a composition containing a quinazolinone derivative represented by a general formula in Claims 6, 13, 16, and 17.

II. Claims 20 and 23, drawn to a method of treating cardiac fibrosis with said composition.

III. Claims 19 and 22, drawn to a method of manufacturing a medicament containing said composition.

The Examiner reasons that Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the claim groups lack a special technical feature in that the claims all relate to a quinazolinone derivative as represented by the disclosed formula that is well known in the art. Applicants traverse this requirement and request consideration of all claims together in this application, for the reasons set forth below.

First, Applicant would like to point out that the Examiner indicates that Group I is comprised of Claims 1-28. However, only Claims 1-23 are currently pending in the present application and Applicant believes that intended Group I claims are those originally referring to a "composition", i.e., Claims 1-18, and 21.

Claims 1-18 and 21 (Group I), have been amended to more clearly define the nature of Applicants' invention. Specifically, independent Claims 1, 8, 16, 17, and 21 (all Group I), have been amended to a method of treating a specified condition. All claims dependent from Claims 1, 8, 16, 17, and 21 have also been amended to recite a method. As such, Claims 1-18 and 21 are directly related to the claims of Group II, i.e., Claims 20 and 23 in that they relate to a specific method for preventing common pathogenic processes that occur as result of tissue trauma.

For the reasons set forth above, Applicants assert that the amendments to Claims 1-18 and 21 essentially eliminates Group I as a distinct group and clarifies that all claims now pending refer to a single inventive concept including the claims of Group III, i.e., Claims 19 and 22, which cover the preparation of a composition specifically adapted to the practice of the methods disclosed in Claims 1-18, 20, 21, and 23. The pending claims as amended all relate to a method and do not represent separate or distinct inventions. The search and examination of all claims together in one application is proper. Accordingly, withdrawal of the restriction requirement is requested.

Conclusion and Provisional Election

Applicants submit that in view of the foregoing amendments, all the claims are seen to relate to a single inventive concept, and the claims are in a form and are of the sort that is properly viewed as relating to a single invention that should not be restricted under PCT Rule 13.1 or 37 C.F.R. §1.141. Applicants therefore request that the restriction and election requirements of the Office Action of December 13, 2001 be reconsidered and withdrawn.

Although, for reasons set forth above in detail, Applicants believe that the reasons for restriction have been obviated by clarifying amendments of a clerical nature, in order to be fully responsive to the Office Action, Applicants provisionally elect for examination the claims of Group II (i.e., Claims 20 and 23). Applicants repeat, however, that it is believed that the amendments above have caused at least Groups I and II to merge.

For the reasons set forth above, entry of the amendments and withdrawal of the restriction requirement set forth in the Office Action of December 13, 2001 are respectfully requested.

Respectfully submitted,

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CERTIFICATE OF MAILING

The undersigned hereby certifies that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on the date indicated below.

02/13/2002
date

Melanie McFadden
Melanie McFadden

CLAIMS AMENDED FOR RESPONSE TO RESTRICTION REQUIREMENT
U.S. Appln. No. 09/762,715 (CGD-004.0P US)(marked)

1. (amended) A [composition] method for regulation of the extracellular matrix economy, comprising the step of administering to a subject in need thereof a pharmaceutically effective amount of an effector in combination with a pharmaceutically acceptable carrier, wherein regulation of the extracellular matrix economy includes inhibition of expression of collagen α1(I) gene, together with inhibition of transcription of NF-κB and inhibition of collagenase type IV production.

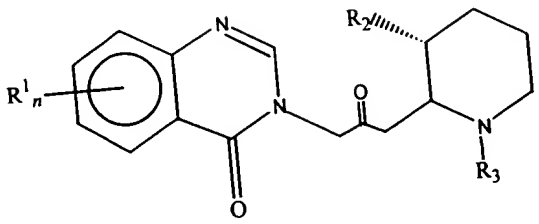
2. (amended) The [composition] method of Claim 1, wherein regulation of the extracellular matrix economy includes inhibition of expression of collagen α1(I) gene and promotion of activity of *cKrox* transcription factor, together with inhibition of transcription of NF-κB and inhibition of collagenase type IV production.

3. (amended) The [composition] method of Claim 2, wherein the regulation of the extracellular matrix economy includes inhibition of expression of collagen α1(I) gene, and promotion of activity of *cKrox*, together with inhibition of transcription of NF-κB and inhibition of collagenase type IV production, and decreasing release of cytokines IL-1β and TNFα, substantially without affecting expression of TGF-β.

4. (amended) The [composition] method of Claim 1, wherein the regulation of the extracellular matrix economy includes decreasing expression of HSP47 in parallel to inhibition of expression of collagen α1(I) gene, inhibition of expression of NF-κB, inhibition of collagenase type IV production, and decreasing release of cytokines IL-1β and TNFα, substantially without affecting an expression of TGF-β.

5. (amended) The [composition] method of any of Claims 1 to 4, wherein said effector is a quinazolinone derivative.

6. (amended) The [composition] method of Claim 5, wherein said quinazolinone derivative is a member of a group having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy, and lower alkoxy, and

R_3 is a member of the group consisting of hydrogen and lower alkenoxy; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

7. (amended) The [composition] method of Claim 6, wherein said compound is Halofuginone and pharmaceutically acceptable salts thereof.

8. (amended) A [composition] method for inhibition of at least one pathological process associated with tissue trauma, comprising the step of administering to a subject in need thereof a pharmaceutically effective amount of an effector in combination with a pharmaceutically acceptable carrier, wherein said effector regulates the extracellular matrix economy in order to inhibit [the] at least one pathological process associated with tissue trauma, wherein regulation of the extracellular matrix economy includes inhibition of expression of collagen α1(I) gene, together with inhibition of transcription of NF-κB and inhibition of collagenase type IV production.

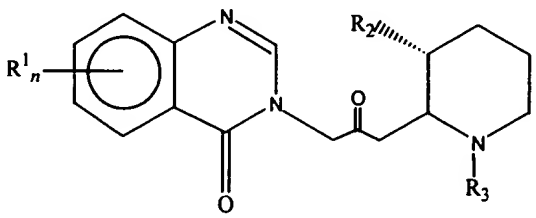
9. (amended) The [composition] method of Claim 8, wherein regulation of the extracellular matrix economy includes inhibition of expression of collagen α1(I) gene and promotion of activity of *cKrox* transcription factor, together with inhibition of transcription of NF-κB and inhibition of collagenase type IV production.

10. (amended) The [composition] method of Claim 9, wherein the regulation of the extracellular matrix economy includes inhibition of expression of collagen α1(I) gene, and promotion of activity of *cKrox*, together with inhibition of transcription of NF-κB, inhibition of collagenase type IV production and decreasing release of cytokines IL-1β and TNFα, substantially without affecting expression of TGF-β.

11. (amended) The [composition] method of Claim 8, wherein said effector decreases an expression of HSP47 in parallel to inhibition of expression of collagen α1(I) gene, inhibits expression of NF-κB, inhibits collagenase type IV production and decreases release of cytokines IL-1β and TNFα, substantially without affecting expression of TGF-β.

12. (amended) The [composition] method of any of Claims 8 to 11, wherein said effector is a quinazolinone derivative.

13. (amended) The [composition] method of Claim 12, wherein said quinazolinone derivative is a member of a group having a formula:



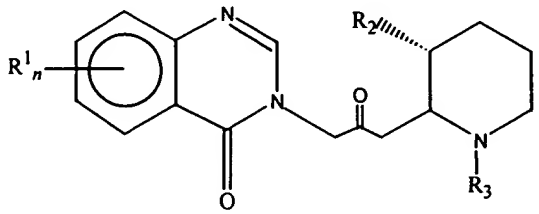
wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;
R_2 is a member of the group consisting of hydroxy, acetoxy, and lower alkoxy, and
R_3 is a member of the group consisting of hydrogen and lower alkenoxy; and
n is either 1 or 2;
and pharmaceutically acceptable salts thereof.

14. (amended) The [composition] method of Claim 13, wherein said effector is Halofuginone and pharmaceutically acceptable salts thereof.

15. (amended) The [composition] method of any of Claims 8 to 14, wherein the at least one pathological process is selected from the group consisting of cancers, fibrotic conditions including but not limited to hepatic fibrosis and cirrhosis, chronic inflammatory disease, renal fibrosis, pulmonary fibrosis, cardiac fibrosis, neo-angiogenesis, formation of adhesion, psoriasis, keloids, hypertrophic scars, and a pathological condition which can be ameliorated, reduced or otherwise treated by an effector capable of regulating the extracellular matrix economy.

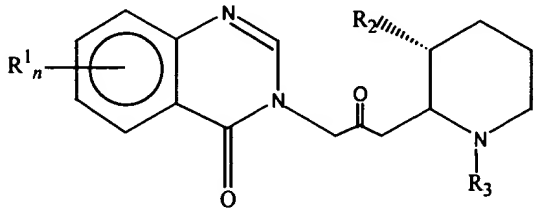
16. (amended) A [composition] method for inhibiting cell proliferation enabled by a deposition of an extracellular matrix, comprising the step of administering to a subject in need thereof a pharmaceutically effective amount of a compound having a formula:



wherein:
R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy, and
R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl;
n is either 1 or 2;
and pharmaceutically acceptable salts thereof.

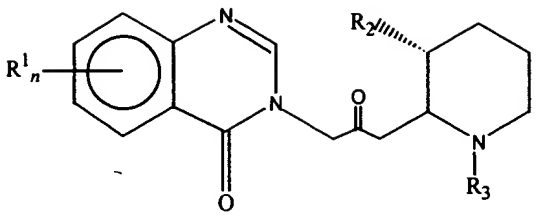
17. (amended) A [composition] method for treating cardiac fibrosis, comprising the step of administering to a subject in need thereof a pharmaceutically effective amount of a compound in combination with a pharmaceutically acceptable carrier, the compound being a member of a group having a formula:



wherein:
R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;
R_2 is a member of the group consisting of hydroxy, acetoxy, and lower alkoxy;
R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and
n is either 1 or 2;
and pharmaceutically acceptable salts thereof.

18. (amended) The [composition] method of Claim 17, wherein the compound is Halofuginone.

19. A method of manufacturing a medicament for treating cardiac fibrosis, comprising the step of placing a pharmaceutically effective amount of a compound in a pharmaceutically acceptable carrier, the compound being a member of a group having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

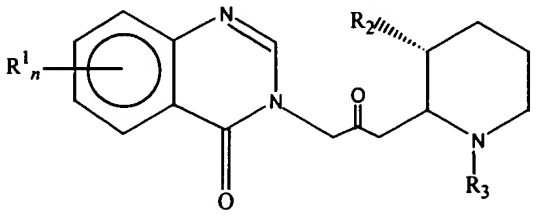
R_2 is a member of the group consisting of hydroxy, acetoxy, and lower alkoxy ;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

20. A method for the treatment of cardiac fibrosis in a subject, comprising the step of administering a pharmaceutically effective amount of a compound having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

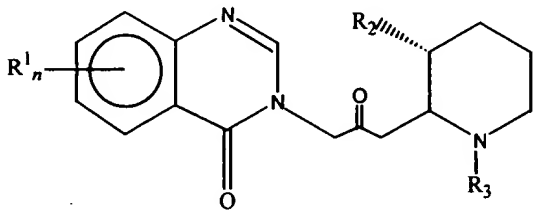
R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy,

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

21. (amended) A [composition] method for substantially preventing cardiac fibrosis, comprising the step of administering to a subject at risk of developing cardiac fibrosis a pharmaceutically effective amount of a compound in combination with a pharmaceutically acceptable carrier, the compound being a member of a group having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

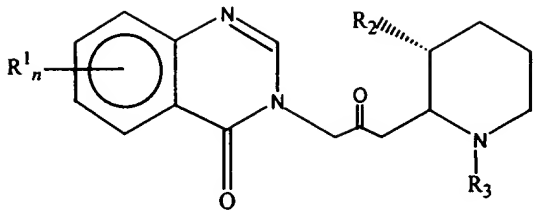
R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

22. A method of manufacturing a medicament for substantially preventing cardiac fibrosis, comprising the step of placing a pharmaceutically effective amount of a compound in a pharmaceutically acceptable carrier, the compound being a member of a group having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

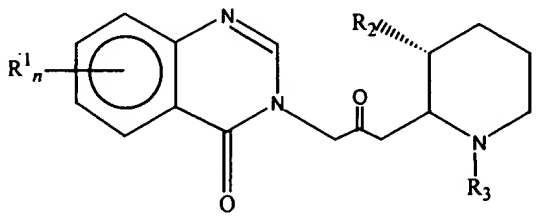
R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

23. A method for substantially preventing cardiac fibrosis in a subject, comprising the step of administering a pharmaceutically effective amount of a compound having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy,

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

CLAIMS AMENDED FOR RESPONSE TO RESTRICTION REQUIREMENT
U.S. Appln. No. 09/762,715 (CGD-004.0P US)(unmarked)

1. (amended) A method for regulation of the extracellular matrix economy, comprising the step of administering to a subject in need thereof a pharmaceutically effective amount of an effector in combination with a pharmaceutically acceptable carrier, wherein regulation of the extracellular matrix economy includes inhibition of expression of collagen α1(I) gene, together with inhibition of transcription of NF-κB and inhibition of collagenase type IV production.

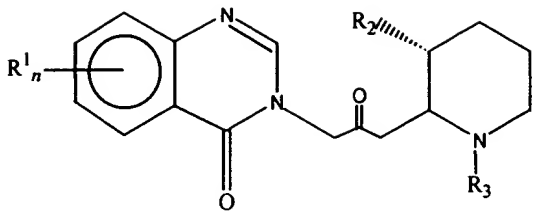
2. (amended) The method of Claim 1, wherein regulation of the extracellular matrix economy includes inhibition of expression of collagen α1(I) gene and promotion of activity of *cKrox* transcription factor, together with inhibition of transcription of NF-κB and inhibition of collagenase type IV production.

3. (amended) The method of Claim 2, wherein the regulation of the extracellular matrix economy includes inhibition of expression of collagen α1(I) gene, and promotion of activity of *cKrox*, together with inhibition of transcription of NF-κB and inhibition of collagenase type IV production, and decreasing release of cytokines IL-1β and TNFα, substantially without affecting expression of TGF-β.

4. (amended) The method of Claim 1, wherein the regulation of the extracellular matrix economy includes decreasing expression of HSP47 in parallel to inhibition of expression of collagen α1(I) gene, inhibition of expression of NF-κB, inhibition of collagenase type IV production, and decreasing release of cytokines IL-1β and TNFα, substantially without affecting an expression of TGF-β.

5. (amended) The method of any of Claims 1 to 4, wherein said effector is a quinazolinone derivative.

6. (amended) The method of Claim 5, wherein said quinazolinone derivative is a member of a group having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy, and lower alkoxy, and

R_3 is a member of the group consisting of hydrogen and lower alkenoxy; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

7. (amended) The method of Claim 6, wherein said compound is Halofuginone and pharmaceutically acceptable salts thereof.

8. (amended) A method for inhibition of at least one pathological process associated with tissue trauma, comprising the step of administering to a subject in need thereof a pharmaceutically effective amount of an effector in combination with a pharmaceutically acceptable carrier, wherein said effector regulates the extracellular matrix economy in order to inhibit at least one pathological process associated with tissue trauma, wherein regulation of the extracellular matrix economy includes inhibition of expression of collagen α1(I) gene, together with inhibition of transcription of NF-κB and inhibition of collagenase type IV production.

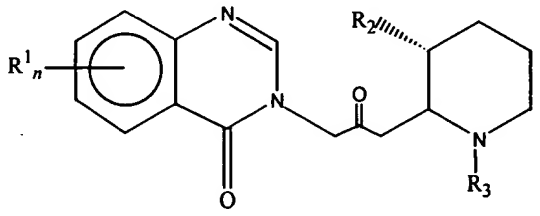
9. (amended) The method of Claim 8, wherein regulation of the extracellular matrix economy includes inhibition of expression of collagen α1(I) gene and promotion of activity of *cKrox* transcription factor, together with inhibition of transcription of NF-κB and inhibition of collagenase type IV production.

10. (amended) The method of Claim 9, wherein the regulation of the extracellular matrix economy includes inhibition of expression of collagen α1(I) gene, and promotion of activity of *cKrox*, together with inhibition of transcription of NF-κB, inhibition of collagenase type IV production and decreasing release of cytokines IL-1β and TNFα, substantially without affecting expression of TGF-β.

11. (amended) The method of Claim 8, wherein said effector decreases an expression of HSP47 in parallel to inhibition of expression of collagen α1(I) gene, inhibits expression of NF-κB, inhibits collagenase type IV production and decreases release of cytokines IL-1β and TNFα, substantially without affecting expression of TGF-β.

12. (amended) The method of any of Claims 8 to 11, wherein said effector is a quinazolinone derivative.

13. (amended) The method of Claim 12, wherein said quinazolinone derivative is a member of a group having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy, and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy; and

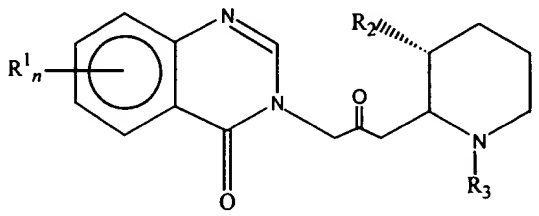
n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

14. (amended) The method of Claim 13, wherein said effector is Halofuginone and pharmaceutically acceptable salts thereof.

15. (amended) The method of any of Claims 8 to 14, wherein the at least one pathological process is selected from the group consisting of cancers, fibrotic conditions including but not limited to hepatic fibrosis and cirrhosis, chronic inflammatory disease, renal fibrosis, pulmonary fibrosis, cardiac fibrosis, neo-angiogenesis, formation of adhesion, psoriasis, keloids, hypertrophic scars, and a pathological condition which can be ameliorated, reduced or otherwise treated by an effector capable of regulating the extracellular matrix economy.

16. (amended) A method for inhibiting cell proliferation enabled by a deposition of an extracellular matrix, comprising the step of administering to a subject in need thereof a pharmaceutically effective amount of a compound having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

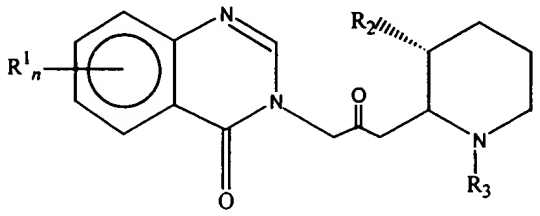
R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl;

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

17. (amended) A method for treating cardiac fibrosis, comprising the step of administering to a subject in need thereof a pharmaceutically effective amount of a compound in combination with a pharmaceutically acceptable carrier, the compound being a member of a group having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy, and lower alkoxy;

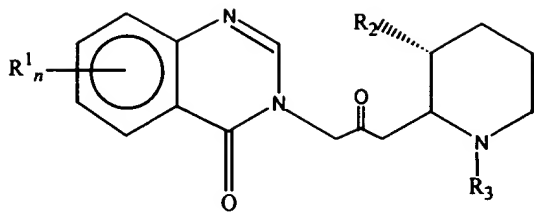
R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

18. (amended) The method of Claim 17, wherein the compound is Halofuginone.

19. A method of manufacturing a medicament for treating cardiac fibrosis, comprising the step of placing a pharmaceutically effective amount of a compound in a pharmaceutically acceptable carrier, the compound being a member of a group having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

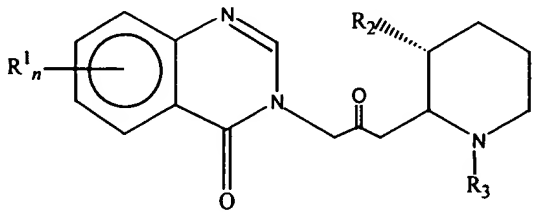
R_2 is a member of the group consisting of hydroxy, acetoxy, and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

20. A method for the treament of cardiac fibrosis in a subject, comprising the step of administering a pharmaceutically effective amount of a compound having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

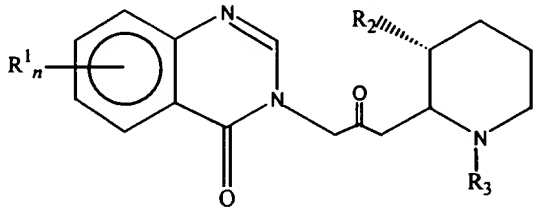
R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy,

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl;

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

21. (Amended) A method for substantially preventing cardiac fibrosis, comprising the step of administering to a subject at risk of developing cardiac fibrosis a pharmaceutically effective amount of a compound in combination with a pharmaceutically acceptable carrier, the compound being a member of a group having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

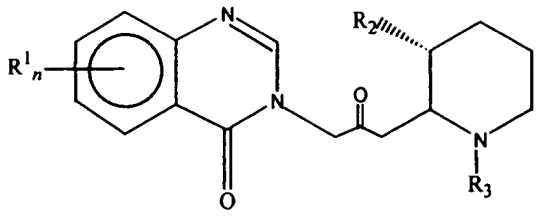
R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

22. A method of manufacturing a medicament for substantially preventing cardiac fibrosis, comprising the step of placing a pharmaceutically effective amount of a compound in a pharmaceutically acceptable carrier, the compound being a member of a group having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

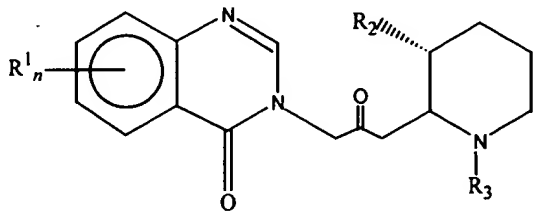
R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.

23. A method for substantially preventing cardiac fibrosis in a subject, comprising the step of administering a pharmaceutically effective amount of a compound having a formula:



wherein:

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl, and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and

n is either 1 or 2;

and pharmaceutically acceptable salts thereof.